Xtandi™ 40 mg
soft capsules
enzalutamide

astellas

1. NAME OF THE MEDICINAL PRODUCT

Xtandi soft capsules 40 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains 40 mg of enzalutamide.

Excipient with known effect:
Each soft capsule contains 57.8 mg of sorbitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Soft capsule.
White to off-white oblong soft capsules (approximately 20 mm x 9 mm) imprinted with "ENZ" in black ink on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Xtandi is indicated for :
• the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) (see section 5.1).

• the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC) (see section 5.1).

• the treatment of adult men with metastatic castration-resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated (see section 5.1).

• the treatment of adult men with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel therapy.

4.2 Posology and method of administration

Posology
The recommended dose is 160 mg enzalutamide (four 40 mg capsules) as a single oral daily dose.

Medical castration with a luteinising hormone-releasing hormone (LHRH) analogue should be continued during treatment of patients not surgically castrated.

Xtandi can be taken with or without food and should be taken at approximately the same time every day. If a patient misses taking Xtandi at the usual time, the prescribed dose should be taken as close as possible to the usual time. If a patient misses a dose for a whole day, treatment should be resumed the following day with the usual daily dose.

If a patient experiences a ≥ Grade 3 toxicity or an intolerable adverse reaction, dosing should be withheld for one week or until symptoms improve to ≤ Grade 2, then resumed at the same or a reduced dose (120 mg or 80 mg) if warranted.

Concomitant use with strong CYP2C8 inhibitors
The concomitant use of strong CYP2C8 inhibitors should be avoided if possible. If patients must be co-administered a strong CYP2C8 inhibitor, the dose of enzalutamide should be reduced to 80 mg once daily. If co-administration of the strong CYP2C8 inhibitor is discontinued, the enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor (see section 4.5).

Elderly
No dose adjustment is necessary for older people (see section 5.1 and 5.2).

Hepatic impairment
No dose adjustment is necessary for patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C, respectively). An increased drug half-life has however been observed in patients with severe hepatic impairment (see section 4.4 and 5.2).

Renal impairment
No dose adjustment is necessary for patients with mild or moderate renal impairment (see section 5.2). Caution is advised in patients with severe renal impairment or end-stage renal disease (see section 4.4).

Paediatric population
There is no relevant use of enzalutamide in the paediatric population in the indication of treatment of adult men with castration-resistant prostate cancer or metastatic hormone-sensitive prostate cancer.

Method of administration
Xtandi is for oral use. The capsules should be swallowed whole with water. Do not chew, dissolve or open.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Women who are or may become pregnant (see section 4.6).

4.4 Special warnings and precautions for use

Risk of seizure
Use of enzalutamide has been associated with events of seizure (see section 4.8). Permanently discontinue enzalutamide in patients who develop a seizure during treatment.

Posterior Reversible Encephalopathy Syndrome
There have been rare reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving Xtandi (see section 4.8). PRES is a rare, reversible, neurological disorder which can present with rapidly evolving symptoms including seizure, headache, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). Discontinuation of Xtandi in patients who develop PRES is recommended.

Hypersensitivity
Hypersensitivity reactions manifested by symptoms including, but not limited to, rash, or face, tongue,

lip, or pharyngeal edema, have been observed with enzalutamide (see section 4.8).

Concomitant use with other medicinal products
Enzalutamide is a potent enzyme inducer and may lead to loss of efficacy of many commonly used medicinal products (see examples in section 4.5). A review of concomitant medicinal products should therefore be conducted when initiating enzalutamide treatment. Concomitant use of enzalutamide with medicinal products that are sensitive substrates of many metabolising enzymes or transporters (see section 4.5) should generally be avoided if their therapeutic effect is of large importance to the patient, and if dose adjustments cannot easily be performed based on monitoring of efficacy or plasma concentrations.

Co-administration with warfarin and coumarin-like anticoagulants should be avoided. If Xtandi is co-administered with an anticoagulant metabolised by CYP2C9 (such as warfarin or acenocoumarol), additional International Normalised Ratio (INR) monitoring should be conducted (see section 4.5).

Renal impairment
Caution is required in patients with severe renal impairment as enzalutamide has not been studied in this patient population.

Severe hepatic impairment
An increased drug half-life has been observed in patients with severe hepatic impairment, possibly related to increased tissue distribution. The clinical relevance of this observation remains unknown. A prolonged time to reach steady state concentrations is however anticipated, and the time to maximum pharmacological effect as well as time for onset and decline of enzyme induction (see section 4.5) may be increased.

Recent cardiovascular disease
The phase 3 studies excluded patients with recent myocardial infarction (in the past 6 months) or unstable angina (in the past 3 months), New York Heart Association Class (NYHA) III or IV heart failure except if Left Ventricular Ejection Fraction (LVEF) ≥ 45%, patients with diagnosed or suspected congenital long QT syndrome, QTcF > 470 ms, bradycardia or uncontrolled hypertension. This should be taken into account if Xtandi is prescribed in these patients.

Use with chemotherapy
The safety and efficacy of concomitant use of Xtandi with cytotoxic chemotherapy has not been established. Co-administration of enzalutamide has no clinically relevant effect on the pharmacokinetics of intravenous docetaxel (see section 4.5); however, an increase in the occurrence of docetaxel-induced neutropenia cannot be excluded.

Excipients
Xtandi contains sorbitol (E420). Patients with rare hereditary problems of fructose intolerance should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Potential for other medicinal products to affect enzalutamide exposures

CYP2C8 inhibitors
CYP2C8 plays an important role in the elimination of enzalutamide and in the formation of its active metabolite. Following oral administration of the strong CYP2C8 inhibitor gemfibrozil (600 mg twice daily) to healthy male subjects, the AUC of enzalutamide increased by 326% while C_{max} of enzalutamide decreased by 18%. For the sum of unbound enzalutamide plus the unbound active metabolite, the AUC increased by 77% while C_{max} decreased by 19%. Strong inhibitors (e.g. gemfibrozil) of CYP2C8 are to be avoided or used with caution during enzalutamide treatment. If patients must be co-administered a strong CYP2C8 inhibitor, the dose of enzalutamide should be reduced to 80 mg once daily (see section 4.2).

CYP3A4 inhibitors
CYP3A4 plays a minor role in the metabolism of enzalutamide. Following oral administration of the strong CYP3A4 inhibitor itraconazole (200 mg once daily) to healthy male subjects, the AUC of enzalutamide increased by 41% while C_{max} was unchanged. For the sum of unbound enzalutamide plus the unbound active metabolite, the AUC increased by 27% while C_{max} was again unchanged. No dose adjustment is necessary when Xtandi is co-administered with inhibitors of CYP3A4.

CYP2C8 and CYP3A4 inducers
Following oral administration of the moderate CYP2C8 and strong CYP3A4 inducer rifampin (600 mg once daily) to healthy male subjects, the AUC of enzalutamide plus the active metabolite decreased by 37% while C_{max} remained unchanged. No dose adjustment is necessary when Xtandi is co-administered with inducers of CYP2C8 or CYP3A4.

Potential for enzalutamide to affect exposures to other medicinal products

Enzyme induction
Enzalutamide is a potent enzyme inducer and increases the synthesis of many enzymes and transporters; therefore, interaction with many common medicinal products that are substrates of enzymes or transporters is expected. The reduction in plasma concentrations can be substantial, and lead to lost or reduced clinical effect. There is also a risk of increased formation of active metabolites. Enzymes that may be induced include CYP3A in the liver and gut, CYP2B6, CYP2C9, CYP2C19, and uridine 5'-diphospho-glucuronosyltransferase (UGTs - glucuronide conjugating enzymes). The transport protein P-gp may also be induced, and probably other transporters as well, e.g. multidrug resistance-associated protein 2 (MRP2), breast cancer resistance protein (BCRP) and the organic anion transporting polypeptide 1B1 (OATP1B1).

In vivo studies have shown that enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Co-administration of enzalutamide (160 mg once daily) with single oral doses of sensitive CYP substrates in prostate cancer patients resulted in an 86% decrease in the AUC of midazolam (CYP3A4 substrate), a 56% decrease in the AUC of S-warfarin (CYP2C9 substrate), and a 70% decrease in the AUC of omeprazole (CYP2C19 substrate). UGT1A1 may have been induced as well. In a clinical study in patients with metastatic CRPC, Xtandi (160 mg once daily) had no clinically relevant effect on the pharmacokinetics of intravenously administered docetaxel (75 mg/m^2 by infusion every 3 weeks). The AUC of docetaxel decreased by 12% [geometric mean ratio (GMR) = 0.882 (90% CI: 0.767, 1.02)] while C_{max} decreased by 4% [GMR = 0.963 (90% CI: 0.834, 1.11)].

Interactions with certain medicinal products that are eliminated through metabolism or active transport are expected. If their therapeutic effect is of large importance to the patient, and dose adjustments are not easily performed based on monitoring of efficacy or plasma concentrations, these medicinal products are to be avoided or used with caution. The risk for liver injury after paracetamol administration is suspected to be higher in patients concomitantly treated with enzyme inducers.

Groups of medicinal products that can be affected include, but are not limited to:

- Analgesics (e.g. fentanyl, tramadol)
- Antibiotics (e.g. clarithromycin, doxycycline)
- Anticancer agents (e.g. cabazitaxel)
- Antiepileptics (e.g. carbamazepine, clonazepam, phenytoin, primidone, valproic acid)
- Antipsychotics (e.g. haloperidol)
- Antithrombotics (e.g. acenocoumarol, warfarin, clopidogrel)
- Betablockers (e.g. bisoprolol, propranolol)
- Calcium channel blockers (e.g. diltiazem, felodipine, nicardipine, nifedipine, verapamil)
- Cardiac glycosides (e.g. digoxin)
- Corticosteroids (e.g. dexamethasone, prednisolone)

- HIV antivirals (e.g. indinavir, ritonavir)
- Hypnotics (e.g. diazepam, midazolam, zolpidem)
- Immunosuppressives (e.g. tacrolimus)
- Proton pump inhibitors (e.g. omeprazole)
- Statins metabolized by CYP3A4 (e.g. atorvastatin, simvastatin)
- Thyroid agents (e.g. levothyroxine)

The full induction potential of enzalutamide may not occur until approximately 1 month after the start of treatment, when steady-state plasma concentrations of enzalutamide are reached, although some induction effects may be apparent earlier. Patients taking medicinal products that are substrates of CYP2B6, CYP3A4, CYP2C9, CYP2C19, or UGT1A1 should be evaluated for possible loss of pharmacological effects (or increase in effects in cases where active metabolites are formed) during the first month of enzalutamide treatment, and dose adjustment should be considered as appropriate. In consideration of the long half-life of enzalutamide (5.8 days, see section 5.2), effects on enzymes may persist for one month or longer after stopping enzalutamide. A gradual dose reduction of the concomitant medicinal product may be necessary when stopping enzalutamide treatment.

CYP1A2 and CYP2C8 substrates
Enzalutamide (160 mg once daily) did not cause a clinically relevant change in the AUC or C_{max} of caffeine (CYP1A2 substrate) or pioglitazone (CYP2C8 substrate). The AUC of pioglitazone increased by 20% while C_{max} decreased by 18%. The AUC and C_{max} of caffeine decreased by 11% and 4%, respectively. No dose adjustment is indicated when a CYP1A2 or CYP2C8 substrate is co-administered with Xtandi.

P-gp substrates
In vitro data indicate that enzalutamide may be an inhibitor of the efflux transporter P-gp. The effect of enzalutamide on P-gp substrates has not been evaluated *in vivo*; however, under conditions of clinical use, enzalutamide may be an inducer of P-gp via activation of the nuclear pregnane receptor (PXR). Medicinal products with a narrow therapeutic range that are substrates for P-gp (e.g. colchicine, dabigatran etexilate, digoxin) should be used with caution when administered concomitantly with Xtandi and may require dose adjustment to maintain optimal plasma concentrations.

BCRP, MRP2, OAT3 and OCT1 substrates
Based on *in vitro* data, inhibition of BCRP and MRP2 (in the intestine), as well as organic anion transporter 3 (OAT3) and organic cation transporter 1 (OCT1) (systemically) cannot be excluded. Theoretically, induction of these transporters is also possible, and the net effect is presently unknown.

<u>Effect of food on enzalutamide exposures</u>
Food has no clinically significant effect on the extent of exposure to enzalutamide. In clinical trials, Xtandi was administered without regard to food.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
There are no human data on the use of Xtandi in pregnancy and this medicinal product is not for use in women of childbearing potential.

Contraception in males and females
It is not known whether enzalutamide or its metabolites are present in semen. A condom is required during and for 3 months after treatment with enzalutamide if the patient is engaged in sexual activity with a pregnant woman. If the patient engages in sexual intercourse with a woman of childbearing potential, a condom and another form of birth control must be used during and for 3 months after treatment. Studies in animals have shown reproductive toxicity (see section 5.3).

Pregnancy
Enzalutamide is not for use in women. Enzalutamide is contraindicated in women who are or may become pregnant (see section 4.3, 5.3 and 6.6). This medicine may cause harm to the unborn child or potential loss of pregnancy if taken by women who are pregnant.

Breast-feeding
Enzalutamide is not for use in women. It is not known if enzalutamide is present in human milk. Enzalutamide and/or its metabolites are secreted in rat milk (see section 5.3).

Fertility
Animal studies showed that enzalutamide affected the reproductive system in male rats and dogs (see section 5.3).

4.7 Effects on ability to drive and use machines

Xtandi may have moderate influence on the ability to drive and use machines as psychiatric and neurologic events including seizures have been reported (see section 4.8). Patients should be advised of the potential risk of experiencing a psychiatric or neurological event while driving or operating machines. No studies to evaluate the effects of enzalutamide on the ability to drive and use machines have been conducted.

4.8 Undesirable effects

Summary of the safety profile
The most common adverse reactions are asthenia/fatigue, hot flush, hypertension fractures, and fall. Other important adverse reactions include cognitive disorder and neutropenia.

Seizure occurred in 0.5% of enzalutamide-treated patients, 0.1% of placebo-treated patients and 0.3% in bicalutamide-treated patients.

Rare cases of posterior reversible encephalopathy syndrome have been reported in enzalutamide-treated patients (see section 4.4).

Tabulated summary of adverse reactions
Adverse reactions observed during clinical studies are listed below by frequency category. Frequency categories are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions identified in controlled clinical trials and post-marketing

MedDRA System organ class	Very common	Common	Uncommon	Not known[1]
Blood and lymphatic system disorders			leucopenia, neutropenia	
General disorders	asthenia, fatigue			
Psychiatric disorders		anxiety	visual hallucinations	
Nervous system disorders		headache, memory impairment, amnesia, disturbance in attention, dysgeusia, restless legs syndrome	cognitive disorder, seizure[7]	posterior reversible encephalopathy syndrome
Reproductive system and breast disorder		gynaecomastia		
Vascular disorders	hot flush, hypertension			
Skin and subcutaneous tissue disorders		dry skin, pruritus		severe skin reactions[8], rash
Musculoskeletal and connective tissue disorders	fractures[6]			myalgia, muscle spasms, muscular weakness, back pain
Injury, poisoning and procedural complications	fall			
Gastrointestinal disorders				nausea, vomiting, diarrhea
Cardiac disorders		ischemic heart disease[2]		
Immune system disorders				face edema[3] tongue edema[4] lip edema[5] pharyngeal edema
Respiratory disorders				interstitial lung disease

1. Adverse reactions of an unknown frequency have been identified during post approval use of enzalutamide. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.
2. As evaluated by narrow SMQs of 'Myocardial Infarction' and 'Other Ischemic Heart Disease' including the following preferred terms observed in at least two patients in randomized placebo-controlled phase 3 studies: angina pectoris, coronary artery disease, myocardial infarctions, acute myocardial infarction, acute coronary syndrome, angina unstable, myocardial ischaemia, and arteriosclerosis coronary artery.
3. Includes events of face edema and swelling face.
4. Includes events of swollen tongue and tongue edema.
5. Includes events of lip swelling and lip edema.

6. Includes all preferred terms with the word 'fracture' in bones.
7. As evaluated by narrow SMQs of 'Convulsions' including convulsion, grand mal convulsion, complex partial seizures, partial seizures, and status epilepticus. This includes rare cases of seizure with complications leading to death.
8. As evaluated by narrow SMQ of 'Severe Cutaneous Adverse Reactions'. Acute generalized exanthematous pustulosis, dermatitis bullous, dermatitis exfoliative generalized, drug reaction with eosinophilia and systemic symptoms, erythema multiforme, exfoliative rash, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and toxic skin eruption have been reported in post-marketing cases.

Description of selected adverse reactions

Seizure
In controlled clinical studies, 22 patients (0.5%) experienced a seizure out of 4168 patients treated with a daily dose of 160 mg enzalutamide, whereas three patients (0.1%) receiving placebo and one patient (0.3%) receiving bicalutamide, experienced a seizure. In the patients who experienced a seizure when treated with enzalutamide, there was one case of seizure where the patient experienced complications resulting in death. Dose appears to be an important predictor of the risk of seizure, as reflected by preclinical data, and data from a dose-escalation study. In the controlled clinical studies, patients with prior seizure or risk factors for seizure were excluded.

In the 9785-CL-0403 (UPWARD) single-arm trial to assess incidence of seizure in patients with predisposing factors for seizures (whereof 1.6% had a history of seizures), 8 of 366 (2.2%) patients treated with enzalutamide experienced a seizure. The median duration of treatment was 9.3 months.

The mechanism by which enzalutamide may lower the seizure threshold is not known but could be related to data from *in vitro* studies showing that enzalutamide and its active metabolite bind to and can inhibit the activity of the GABA-gated chloride channel.

Ischemic Heart Disease
In randomized placebo-controlled clinical studies, ischemic heart disease occurred in 3.7% of patients treated with enzalutamide plus ADT compared to 1.5 % patients treated with placebo plus ADT. Fifteen (0.4%) patients treated with enzalutamide and 2 (0.1%) patients treated with placebo had an ischemic heart disease event that led to death.

4.9 Overdose

There is no antidote for enzalutamide. In the event of an overdose, treatment with enzalutamide should be stopped and general supportive measures initiated taking into consideration the half-life of 5.8 days. Patients may be at increased risk of seizures following an overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: hormone antagonists and related agents, anti-androgens, ATC code: L02BB04

Mechanism of action
Prostate cancer is known to be androgen sensitive and responds to inhibition of androgen receptor signalling. Despite low or even undetectable levels of serum androgen, androgen receptor signalling continues to promote disease progression. Stimulation of tumour cell growth via the androgen receptor requires nuclear localization and DNA binding. Enzalutamide is a potent androgen receptor signalling inhibitor that blocks several steps in the androgen receptor signalling pathway. Enzalutamide competitively inhibits androgen binding to androgen receptors; and consequently, inhibits nuclear translocation of activated receptors and inhibits the association of the activated androgen receptor with DNA even in the setting of androgen receptor overexpression and in prostate cancer cells resistant to anti-androgens. Enzalutamide treatment decreases the growth of prostate cancer cells and can induce

cancer cell death and tumour regression. In preclinical studies enzalutamide lacks androgen receptor agonist activity.

Pharmacodynamic effects
In a phase 3 clinical trial (AFFIRM) of patients who failed prior chemotherapy with docetaxel, 54% of patients treated with enzalutamide, versus 1.5% of patients who received placebo, had at least a 50% decline from baseline in PSA levels.

In another phase 3 clinical trial (PREVAIL) in chemo-naïve patients, patients receiving enzalutamide demonstrated a significantly higher total PSA response rate (defined as a ≥ 50% reduction from baseline), compared with patients receiving placebo, 78.0% versus 3.5% (difference = 74.5%, $p < 0.0001$).

In a phase 2 clinical trial (TERRAIN) in chemo-naïve patients, patients receiving enzalutamide demonstrated a significantly higher total PSA response rate (defined as a ≥ 50% reduction from baseline), compared with patients receiving bicalutamide, 82.1% versus 20.9% (difference = 61.2%, $p < 0.0001$)

In the MDV3100-09 clinical trial (STRIVE) of non-metastatic and metastatic CRPC, patients receiving enzalutamide demonstrated a significantly higher total confirmed PSA response rate (defined as a ≥ 50% reduction from baseline) compared with patients receiving bicalutamide, 81.3% versus 31.3% (difference = 50.0%, $p < 0.0001$).

In the MDV3100-14 clinical trial (PROSPER) of non-metastatic CRPC, patients receiving enzalutamide demonstrated a significantly higher confirmed PSA response rate (defined as a ≥ 50% reduction from baseline), compared with patients receiving placebo, 76.3% versus 2.4% (difference = 73.9%, $p < 0.0001$).

Clinical efficacy and safety
Efficacy of enzalutamide was established in three randomized, placebo-controlled, multicentre phase 3 clinical studies [MDV3100-14 (PROSPER), CRPC2 (AFFIRM), MDV3100-03 (PREVAIL)] of patients with progressive prostate cancer who had disease progression on androgen deprivation therapy (LHRH analogue or after bilateral orchiectomy). The PREVAIL study enrolled metastatic CRPC chemotherapy-naive patients; whereas the AFFIRM study enrolled metastatic CRPC patients who had received prior docetaxel; and the PROSPER study enrolled patients with non-metastatic CRPC. Additionally, patients with mHSPC were enrolled in the ARCHES study. All patients continued on a LHRH analogue or had prior bilateral orchiectomy. In the active treatment arm, Xtandi was administered orally at a dose of 160 mg daily. In the four clinical trials, patients received placebo in the control arm and patients were allowed, but not required, to take prednisone (maximum daily dose allowed was 10 mg prednisone or equivalent).

Changes in PSA serum concentration independently do not always predict clinical benefit. Therefore, in the four studies it was recommended that patients be maintained on their study treatments until discontinuation criteria were met as specified below for each study.

9785-CL-0335 (ARCHES) Study (patients with metastatic HSPC)
The ARCHES study enrolled 1150 patients with mHSPC, randomized 1:1 to receive treatment with enzalutamide plus ADT or placebo plus ADT (ADT defined as LHRH analogue or bilateral orchiectomy). Patients received enzalutamide at 160 mg once daily (N = 574) or placebo (N = 576).

The demographic and baseline characteristics were well balanced between the two treatment groups. The median age at randomization was 70 years in both treatment groups. Most patients in the total population were Caucasian (80.5%), 13.5% were Asian, and 1.4% were Black.

Radiographic progression-free survival (rPFS) was the primary endpoint defined as the time from randomization to the first objective evidence of radiographic disease progression or death (any cause from time of randomization through 24 weeks after study drug discontinuation), whichever occurred first. Key secondary efficacy endpoints assessed in the study were time to PSA progression, time to start of new antineoplastic therapy, PSA undetectable rate (decline to < 0.2 µg/L), objective response rate (RECIST 1.1) based on independent review, time to deterioration of urinary symptoms, and overall survival. See Table 2 below.

Enzalutamide demonstrated a statistically significant 61% reduction in the risk of an rPFS event compared to placebo [hazard ratio (HR) = 0.39 (95% CI: 0.30, 0.50); p < 0.0001]. The median time to an rPFS event was not reached in the enzalutamide plus ADT arm and was 19.0 months (95% CI: 16.6, 22.2) in the placebo plus ADT arm.

Table 2. Summary of efficacy results in patients treated with either enzalutamide plus ADT or placebo plus ADT in the ARCHES study (intent-to-treat analysis)

	Enzalutamide plus ADT (N = 574)	**Placebo plus ADT (N = 576)**
Primary Endpoint		
Radiographic Progression-free Survival		
Number of events (%)	91 (15.9)	201 (34.9)
Median, months (95% CI)[1]	NR	19.0 (16.6, 22.2)
Hazard ratio (95% CI)[2]	0.39 (0.30, 0.50)	
P-value[2]	p < 0.0001	
Selected Secondary Endpoints		
Time to PSA Progression[3]		
Number of events (%)	45 (7.8)	189 (32.8)
Median, months (95% CI)	NR	NR (16.6, NR)
Hazard ratio (95% CI)[2]	0.19 (0.13, 0.26)	
P-value[2]	p < 0.0001	
Time to Start of New Antineoplastic Therapy		
Number of events (%)	46 (8.0)	133 (23.1)
Median, months (95% CI)[2]	30.2 (NR, NR)[4]	NR (21.1, NR)
Hazard ratio (95% CI)[2]	0.28 (0.20, 0.40)	
P-value[2]	p < 0.0001	
PSA Undetectable Rates		
Patients with PSA detectable at baseline	511	506
Patients with PSA undetectable at baseline	63	70
Undetectable PSA during treatment period	348/511 (68.1)	89/506 (17.6)
95% CI for rate	(63.9, 72.1)	(14.4, 21.2)
Difference in rate (95% CI)[2]	50.5% (45.3, 55.7)	
P-value	p < 0.0001	
Objective Response Rate		
Patients with measurable disease at baseline, n	177	182
Number of events (%)	147 (83.1)	116 (63.7)
95% CI for rate	(76.7, 88.3)	(56.3, 70.7)
Difference in rate (95% CI)[2]	19.3% (10.4, 28.2)	
P-value	p < 0.0001	

NR = Not reached

1. Calculated using Brookmeyer and Crowley method
2. Stratified by volume of disease (low vs high) and prior docetaxel use (yes or no)
3. PSA progression was defined as a ≥25% increase and an absolute increase of ≥2 µg/L above nadir

4. While an estimate of the median time was provided for the enzalutamide plus ADT arm (30.2 months), this estimate was not reliable as it resulted from an event observed in the only remaining patient at risk at approximately 30 months, leading to a vertical drop at the end of the Kaplan-Meier curve.

Figure 1. Kaplan-Meier curve of rPFS in ARCHES study (intent-to-treat analysis)

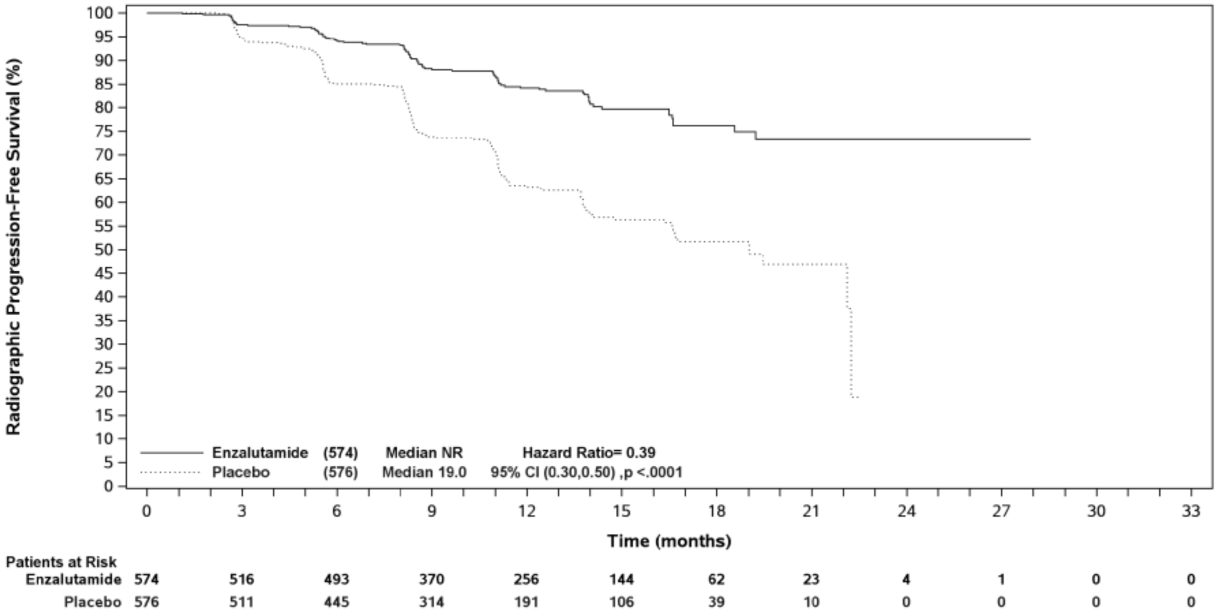
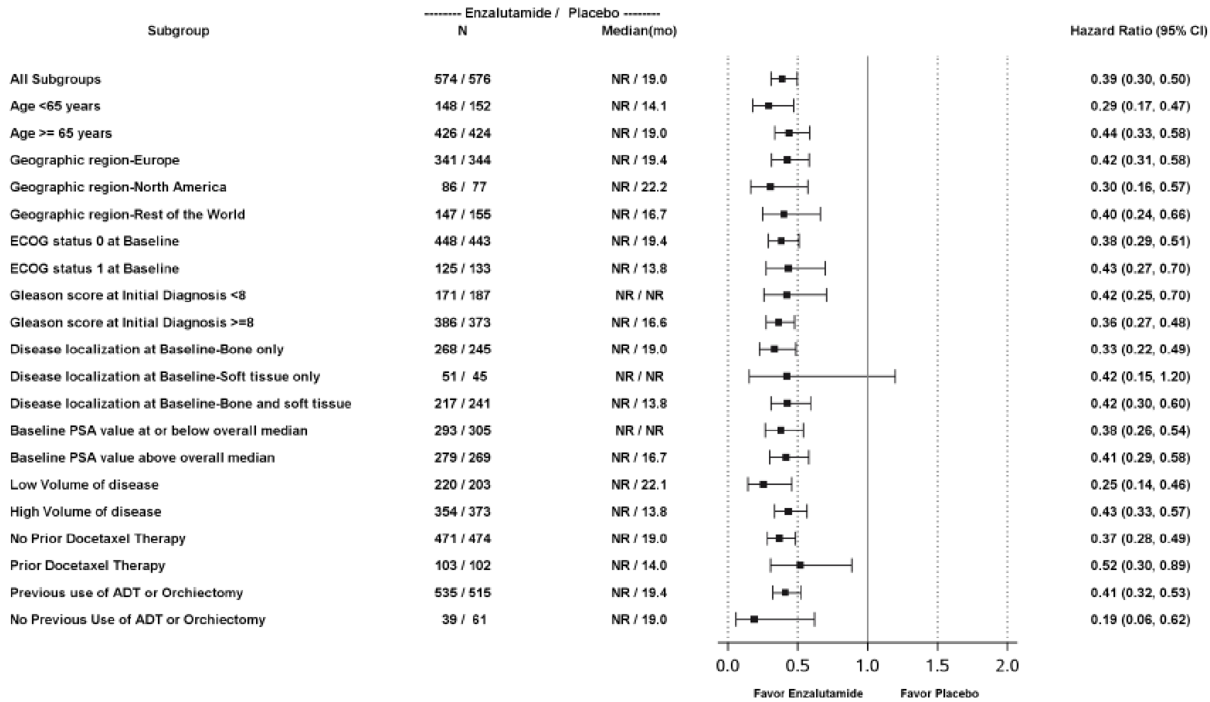


Figure 2. Forest plot of rPFS by prespecified subgroup in ARCHES (intent-to-treat analysis)



Enzalutamide demonstrated a statistically significant 81.0% reduction in the risk of PSA progression compared with placebo [HR = 0.19 (95% CI: 0.13, 0.26); p < 0.0001]. The median time (95% CI) was not reached for enzalutamide or placebo.

Enzalutamide demonstrated a statistically significant 72% reduction in risk of initiation of a new antineoplastic therapy compared to placebo [HR = 0.28 (95% CI: 0.20, 0.40); p < 0.0001].

Enzalutamide significantly increased the chance of a PSA decline to an undetectable rate (< 0.2 μg/L) compared to treatment with placebo. The PSA undetectable rate was 68.1% for enzalutamide and 17.6% for placebo plus ADT. The rate difference is statistically significant [50.5% (95% CI: 45.3, 55.7); p < 0.0001].

Objective response rate (calculated as percentage of patients with measurable disease at baseline who achieved a complete or partial response in their soft tissue disease) was 83.1% for patients in the enzalutamide treatment arm and 63.7% in the placebo arm. Enzalutamide demonstrated a statistically significant 19.3% difference in objective response rate compared to placebo.

The first pre-specified interim analysis for overall survival was conducted at the time of the rPFS analysis. At the time of the first interim analysis, overall survival data were not mature and did not show a statistically significant difference in patients treated with enzalutamide compared to placebo [HR = 0.81 (95% CI: 0.53, 1.25) p = 0.3361]. The median overall survival was not reached in either treatment group.

ANZUP 1304 (ENZAMET) Study (patients with metastatic HSPC)
The ENZAMET study enrolled 1125 patients with mHSPC randomized 1:1 to receive treatment orally once daily with enzalutamide 160 mg (N = 563) or nonsteroidal anti-androgen (NSAA, N = 562). All patients in the trial received a LHRH analog or had a prior bilateral orchiectomy. Patients were stratified by volume of disease (low vs high), concomitant antiresorptive therapy (yes vs no), comorbidities (ACE-27: 0 to 1 vs 2 to 3) and planned use of a total of 6 cycles of docetaxel, of which 0-2 cycles were allowed before randomization (yes vs no). Patients were required to have confirmation of metastatic prostate cancer by positive bone scan or metastatic lesions on CT or MRI scan. Patients continued treatment until evidence of clinical progression via CT, MRI or whole body bone scan.

The following patient demographics and baseline characteristics were balanced between the two treatment arms. The median age at randomization was 69 years in the enzalutamide group and 68 years in the NSAA group (treated with bicalutamide, nilutamide, or flutamide). The majority of patients had an ECOG performance status score of 0 (72%) and a Gleason score of ≥ 8 (58%). Forty-eight percent (48%) of patients had a low volume of disease and 52% of patients had a high volume of disease. High volume of disease is defined as metastases involving the viscera or, in the absence of visceral lesions, there must be 4 or more bone lesions, at least 1 of which must be in a bony structure beyond the vertebral column and pelvic bone. Ten percent (10%) of patients had concomitant antiresorptive therapy, 75% had no or mild comorbidities (ACE-27 score of 0 to 1) and 45% had a total of 6 cycles of docetaxel, of which 0-2 cycles were allowed before randomization.

At the time of analysis, the median follow-up for OS was 33.8 months. The interim analysis demonstrated a statistically significant 33% reduction in the risk of death for patients treated with enzalutamide compared to conventional NSAA treatment [HR of 0.67 (95% CI: 0.52, 0.86; p = 0.0018)].

Figure 3. Kaplan-Meier curves of overall survival (intent-to-treat analysis)

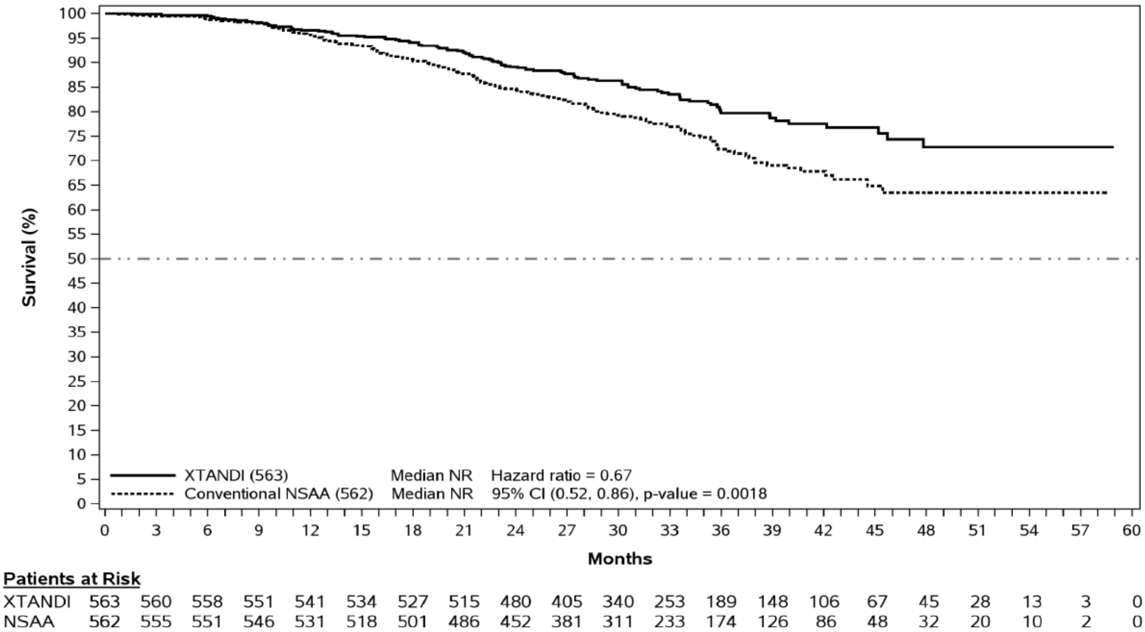
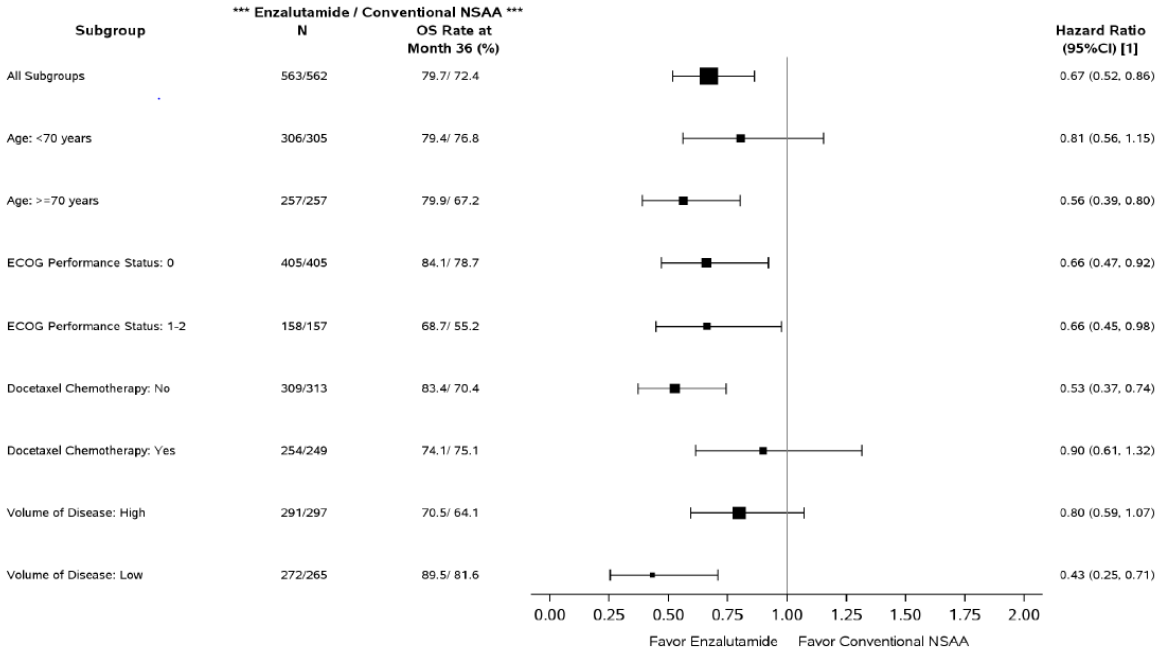


Figure 4. Forest plot of overall survival by subgroup analysis in the ENZAMET study (intent-to-treat analysis)



MDV3100-14 (PROSPER) study (patients with non-metastatic CRPC)

The PROSPER study enrolled 1401 patients with asymptomatic, high-risk non-metastatic CRPC who continued on androgen deprivation therapy (ADT; defined as LHRH analogue or prior bilateral orchiectomy). Patients were required to have a PSA doubling time ≤ 10 months, PSA ≥ 2 ng/mL, and confirmation of non-metastatic disease by blinded independent central review (BICR).

Patients with a history of mild to moderate heart failure (NYHA Class I or II), and patients taking medicinal products associated with lowering the seizure threshold were allowed. Patients were excluded with a previous history of seizure, a condition that might predispose them to seizure, or certain prior treatments for prostate cancer (i.e., chemotherapy, ketoconazole, abiraterone acetate, aminoglutethimide and/or enzalutamide).

Patients were randomised 2:1 to receive either enzalutamide at a dose of 160 mg once daily (N = 933) or placebo (N = 468). Patients were stratified by Prostate Specific Antigen (PSA) Doubling Time (PSADT) (< 6 months or ≥ 6 months) and the use of bone-targeting agents.

The demographic and baseline characteristics were well-balanced between the two treatment arms. The median age at randomisation was 74 years in the enzalutamide arm and 73 years in the placebo arm. Most patients (approximately 71%) in the study were Caucasian; 16% were Asian and 2% were Black. Eighty-one percent (81%) of patients had an ECOG performance status score of 0 and 19% patients had an ECOG performance status of 1.

Metastasis-free survival (MFS) was the primary endpoint defined as the time from randomisation to radiographic progression or death within 112 days of treatment discontinuation without evidence of radiographic progression, whichever occurred first. Key secondary endpoints assessed in the study were time to PSA progression, time to first use of new antineoplastic therapy (TTA), overall survival (OS). Additional secondary endpoints included time to first use of cytotoxic chemotherapy and chemotherapy-free survival. See results below (Table 3).

Enzalutamide demonstrated a statistically significant 71% reduction in the relative risk of radiographic progression or death compared to placebo [HR = 0.29 (95% CI: 0.24, 0.35), p < 0.0001]. Median MFS was 36.6 months (95% CI: 33.1, NR) on the enzalutamide arm versus 14.7 months (95% CI: 14.2, 15.0) on the placebo arm. Consistent MFS results were also observed in all pre-specified patient subgroups including PSADT (< 6 months or ≥ 6 months), demographic region (North America, Europe, rest of world), age (< 75 or ≥ 75), use of a prior bone-targeting agent.

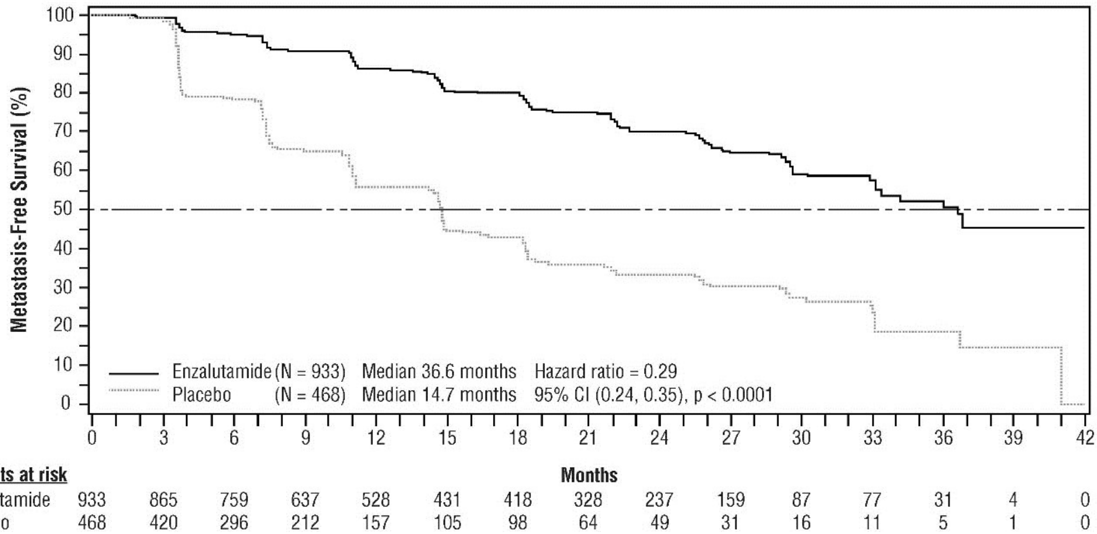
Table 3. Summary of efficacy results in the PROSPER study (intent-to-treat analysis)

	Enzalutamide N = 933	**Placebo N = 468**
Primary Endpoint		
Metastasis-free survival		
Number of Events (%)	219 (23.5)	228 (48.7)
Median, months (95% CI)[1]	36.6 (33.1, NR)	14.7 (14.2, 15.0)
Hazard Ratio (95% CI)[2]	0.29 (0.24, 0.35)	
P-value[3]	p < 0.0001	
Key Secondary Efficacy Endpoints		
Overall Survival[4]		
Number of Events (%)	288 (30.9)	178 (38.0)
Median, months (95% CI)[1]	67.0 (64.0, NR)	56.3 (54.4, 63.0)
Hazard Ratio (95% CI)[2]	0.734 (0.608, 0.885)	
P-value[3]	p = 0.0011	
Time to PSA progression		
Number of Events (%)	208 (22.3)	324 (69.2)
Median, months (95% CI)[1]	37.2 (33.1, NR)	3.9 (3.8, 4.0)
Hazard Ratio (95% CI)[2]	0.07 (0.05, 0.08)	
P-value[3]	p < 0.0001	
Time to first use of new antineoplastic therapy		
Number of Events (%)	142 (15.2)	226 (48.3)
Median, months (95% CI)[1]	39.6 (37.7, NR)	17.7 (16.2, 19.7)
Hazard Ratio (95% CI)[2]	0.21 (0.17, 0.26)	
P-value[3]	p < 0.0001	

NR = Not reached.
1. Based on Kaplan-Meier estimates.

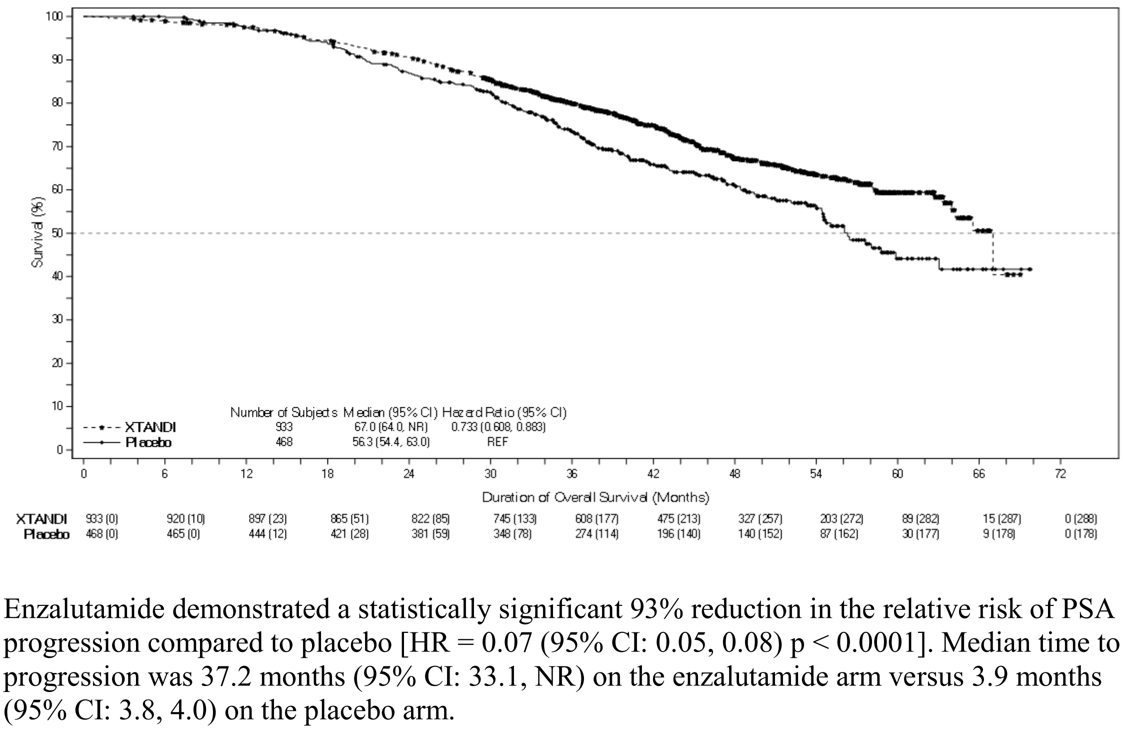
2. HR is based on a Cox regression model (with treatment as the only covariate) stratified by PSA doubling time and prior or concurrent use of a bone targeting agent. The HR is relative to placebo with < 1 favouring enzalutamide.
3. P-value is based on a stratified log-rank test by PSA doubling time (< 6 months, ≥ 6 months) and prior or concurrent use of a bone targeting agent.
4. Based upon a prespecified interim analysis with data cutoff date of 15 Oct 2019.

Figure 5. Kaplan-Meier curves of metastasis-free survival in the PROSPER study (intent-to-treat analysis)



At the final analysis for overall survival, conducted when 466 deaths were observed, a statistically significant improvement in overall survival was demonstrated in patients randomised to receive enzalutamide compared with patients randomised to receive placebo with a 26.6% reduction in risk of death [HR = 0.734, (95% CI: 0.608; 0.885), p = 0.0011]. The median follow-up time was 48.6 and 47.2 months for the enzalutamide and placebo groups, respectively. Thirty-three percent of enzalutamide-treated and 65% of placebo-treated patients received at least one subsequent antineoplastic therapy that may prolong overall survival.

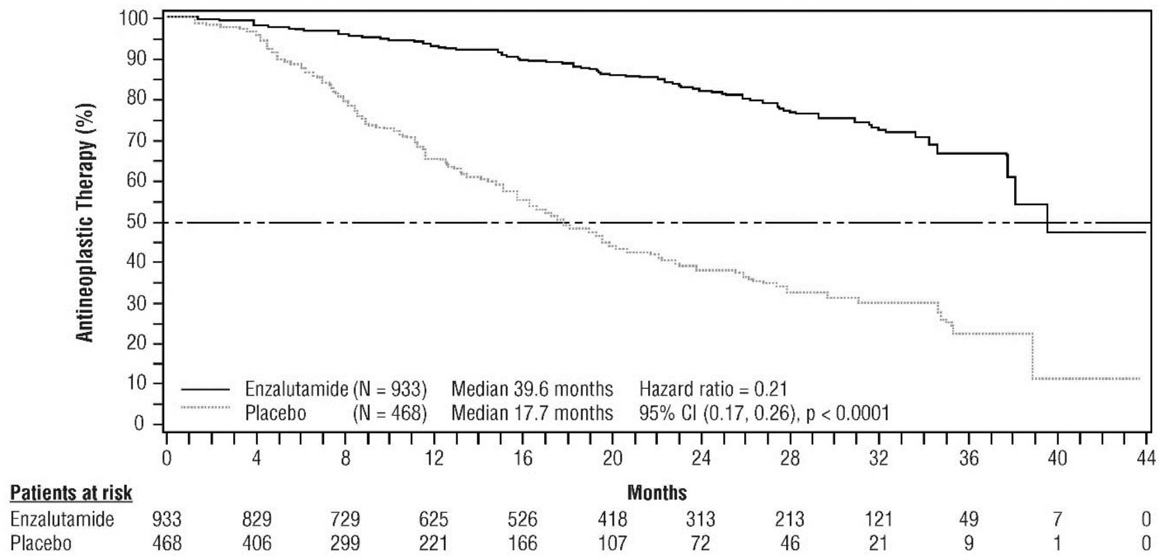
Figure 6. Kaplan-Meier Curves of overall survival in the PROSPER study (intent-to-treat analysis)



Enzalutamide demonstrated a statistically significant 93% reduction in the relative risk of PSA progression compared to placebo [HR = 0.07 (95% CI: 0.05, 0.08) p < 0.0001]. Median time to PSA progression was 37.2 months (95% CI: 33.1, NR) on the enzalutamide arm versus 3.9 months (95% CI: 3.8, 4.0) on the placebo arm.

Enzalutamide demonstrated a statistically significant delay in the time to first use of new antineoplastic therapy compared to placebo [HR = 0.21 (95% CI: 0.17, 0.26), p < 0.0001]. Median time to first use of new antineoplastic therapy was 39.6 months (95% CI: 37.7, NR) on the enzalutamide arm versus 17.7 months (95% CI: 16.2, 19.7) on the placebo arm.

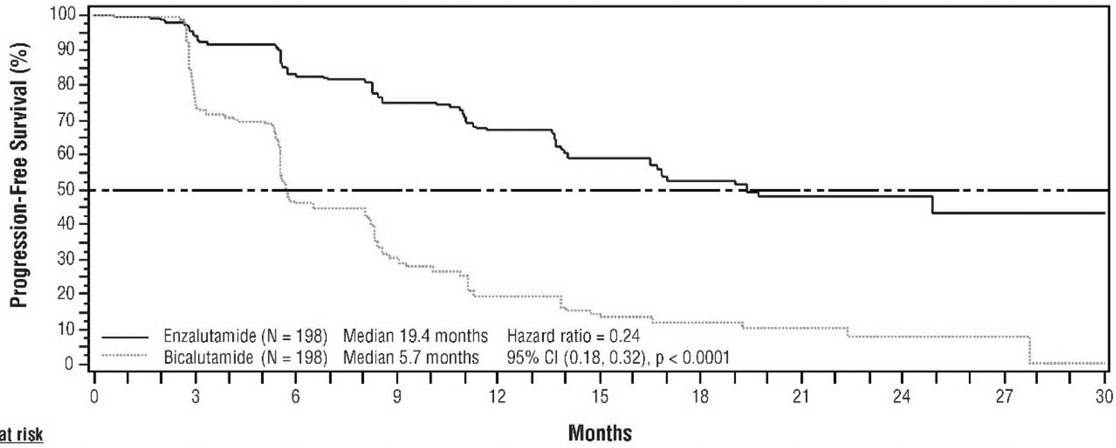
Figure 7. Kaplan-Meier curves of time to first use of new antineoplastic therapy in the PROSPER study (intent-to-treat analysis)



MDV3100-09 (STRIVE) study (chemotherapy- naïve patients with non-metastatic/metastatic CRPC)

The STRIVE study enrolled 396 non-metastatic or metastatic CRPC patients who had serologic or radiographic disease progression despite primary androgen deprivation therapy who were randomised to receive either enzalutamide at a dose of 160 mg once daily (N = 198) or bicalutamide at a dose of 50 mg once daily (N = 198). PFS was the primary endpoint defined as the time from randomisation to the earliest objective evidence of radiographic progression, PSA progression, or death on study. Median PFS was 19.4 months (95% CI: 16.5, not reached) in the enzalutamide group versus 5.7 months (95% CI: 5.6, 8.1) in the bicalutamide group [HR = 0.24 (95% CI: 0.18, 0.32), p < 0.0001]. Consistent benefit of enzalutamide over bicalutamide on PFS was observed in all pre-specified patient subgroups. For the non-metastatic subgroup (N = 139) a total of 19 out of 70 (27.1%) patients treated with enzalutamide and 49 out of 69 (71.0%) patients treated with bicalutamide had PFS events (68 total events). The hazard ratio was 0.24 (95% CI: 0.14, 0.42) and the median time to a PFS event was not reached in the enzalutamide group versus 8.6 months in the bicalutamide group.

Figure 8. Kaplan-Meier curves of progression-free survival in the STRIVE study (intent-to-treat analysis)



Patients at risk											
Enzalutamide	198	171	150	131	101	66	43	24	16	5	0
Bicalutamide	198	138	80	51	29	17	9	5	3	1	0

9785-CL-0222 (TERRAIN) study (chemotherapy-naïve patients with metastatic CRPC)

The TERRAIN study enrolled 375 chemo- and antiandrogen-therapy naïve patients with metastatic castration-resistant prostate cancer who were randomized to receive either enzalutamide at a dose of 160 mg once daily (N = 184) or bicalutamide at a dose of 50 mg once daily (N = 191). Median PFS was 15.7 months for patients on enzalutamide versus 5.8 months for patients on bicalutamide [HR = 0.44 (95% CI: 0.34, 0.57), p < 0.0001]. Progression-free survival was defined as objective evidence of radiographic disease progression by independent central review, skeletal-related events, initiation of new antineoplastic therapy or death by any cause, whichever occurred first. Consistent PFS benefit was observed across all pre-specified patient subgroups.

MDV3100-03 (PREVAIL) study (chemotherapy-naïve patients with metastatic CRPC)

A total of 1717 asymptomatic or mildly symptomatic chemotherapy-naive patients were randomized 1:1 to receive either enzalutamide orally at a dose of 160 mg once daily (N = 872) or placebo orally once daily (N = 845). Patients with visceral disease, patients with a history of mild to moderate heart failure (NYHA Class I or II), and patients taking medications associated with lowering the seizure threshold were allowed. Patients with a previous history of seizure or a condition that might predispose to seizure and patients with moderate or severe pain from prostate cancer were excluded. Study treatment continued until disease progression (evidence of radiographic progression, a skeletal related event, or clinical progression) and the initiation of either a cytotoxic chemotherapy or an investigational agent, or until unacceptable toxicity.

Patient demographics and baseline disease characteristics were balanced between the treatment arms. The median age was 71 years (range 42-93) and the racial distribution was 77% Caucasian, 10% Asian, 2% Black and 11% other or unknown races. Sixty-eight percent (68%) of patients had an ECOG performance status score of 0 and 32% patients had an ECOG performance status of 1. Baseline pain assessment was 0-1 (asymptomatic) in 67% of patients and 2-3 (mildly symptomatic) in 32% of patients as defined by the Brief Pain Inventory Short Form (worst pain over past 24 hours on a scale of 0 to 10). Approximately 45% of patients had measurable soft tissue disease at study entry, and 12% of patients had visceral (lung and/or liver) metastases.

Co-primary efficacy endpoints were overall survival and radiographic progression-free survival (rPFS). In addition to the co-primary endpoints, benefit was also assessed using time to initiation of cytotoxic chemotherapy, best overall soft tissue response, time to first skeletal-related event, PSA response (≥ 50% decrease from baseline), time to PSA progression, and time to FACT-P total score degradation.

Radiographic progression was assessed with the use of sequential imaging studies as defined by Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria (for bone lesions) and/or Response Evaluation Criteria in Solid Tumors (RECIST v 1.1) criteria (for soft tissue lesions). Analysis of rPFS utilized centrally-reviewed radiographic assessment of progression.

At the pre-specified interim analysis for overall survival when 540 deaths were observed, treatment with enzalutamide demonstrated a statistically significant improvement in overall survival compared to treatment with placebo with a 29% reduction in risk of death [HR=0.71, (95% CI: 0.60; 0.84), p < 0.0001]. An updated survival analysis was conducted when 784 deaths were observed. Results from this analysis were consistent with those from the interim analysis (Table 4, Figure 9). At the updated analysis 52% of enzalutamide-treated and 81% of placebo-treated patients had received subsequent therapies for metastatic CRPC that may prolong overall survival.

A final analysis of 5-year PREVAIL data showed a statistically significant increase in overall survival was maintained in patients treated with enzalutamide compared to placebo [HR = 0.835, (95% CI: 0.75, 0.93); p = 0.0008] despite 28% of patients on placebo crossing over to enzalutamide. The 5-year OS rate was 26% for the enzalutamide arm compared to 21% for the placebo arm.

Table 4: Overall survival of patients treated with either enzalutamide or placebo in the PREVAIL study (intent-to-treat analysis)

	Enzalutamide (N = 872)	**Placebo (N = 845)**
Pre-specified interim analysis		
Number of deaths (%)	241 (27.6%)	299 (35.4%)
Median survival, months (95% CI)	32.4 (30.1, NR)	30.2 (28.0, NR)
P-value[1]	p < 0.0001	
Hazard ratio (95% CI)[2]	0.71 (0.60, 0.84)	
Updated survival analysis		
Number of deaths (%)	368 (42.2%)	416 (49.2%)
Median survival, months (95% CI)	35.3 (32.2, NR)	31.3 (28.8, 34.2)
P-value[1]	p = 0.0002	
Hazard ratio (95% CI)[2]	0.77 (0.67, 0.88)	
5-year survival analysis		
Number of deaths (%)	689 (79)	693 (82)
Median survival, months (95% CI)	35.5 (33.5, 38.0)	31.4 (28.9, 33,8)
P-value[1]	p = 0.0008	
Hazard ratio (95% CI)[2]	0.835 (0.75, 0.93)	

1. P-value is derived from an unstratified log-rank test
2. Hazard ratio is derived from an unstratified proportional hazards model. Hazard ratio <1 favours enzalutamide

NR, not reached.

Figure 9: Kaplan-Meier curves of overall survival based on 5-year survival analysis in the PREVAIL study (intent-to-treat analysis)

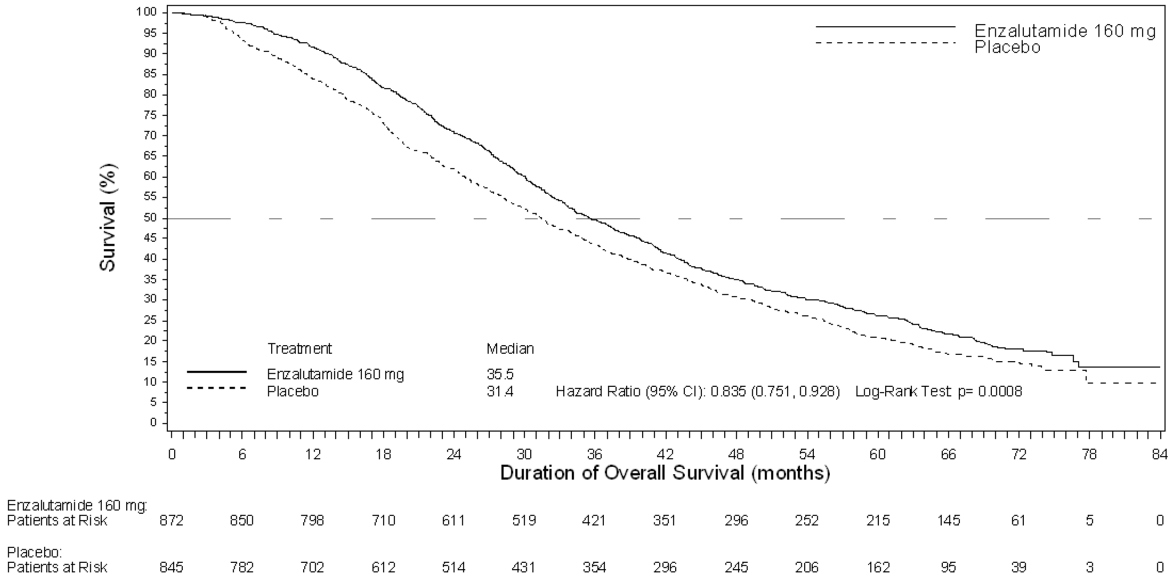
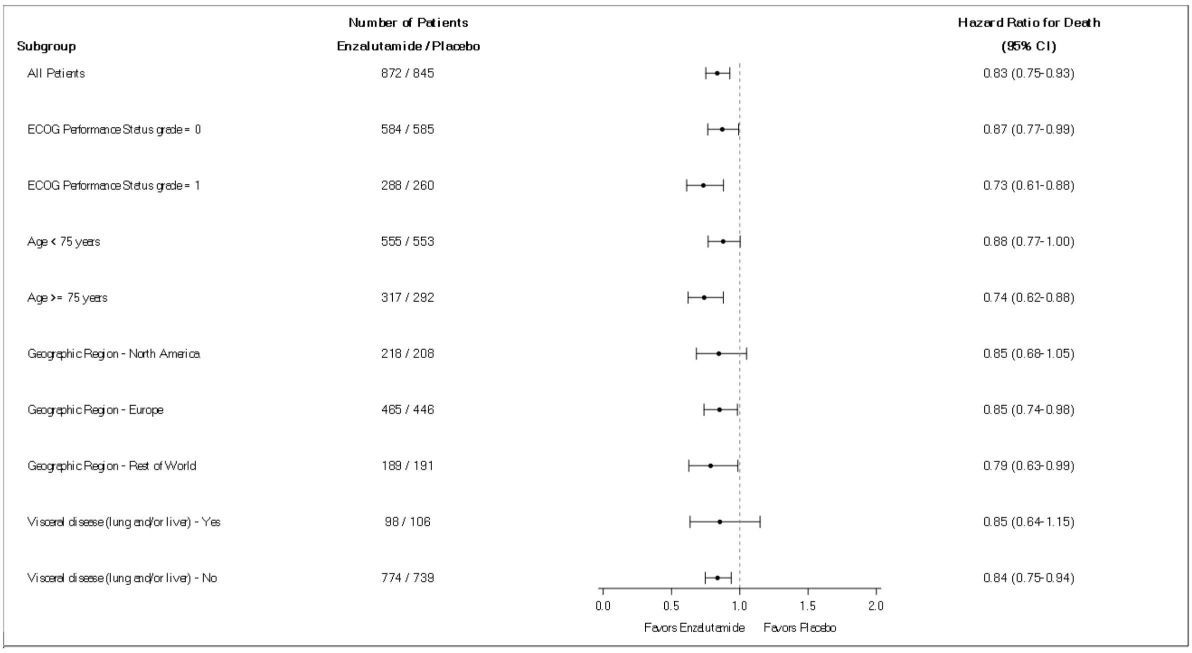
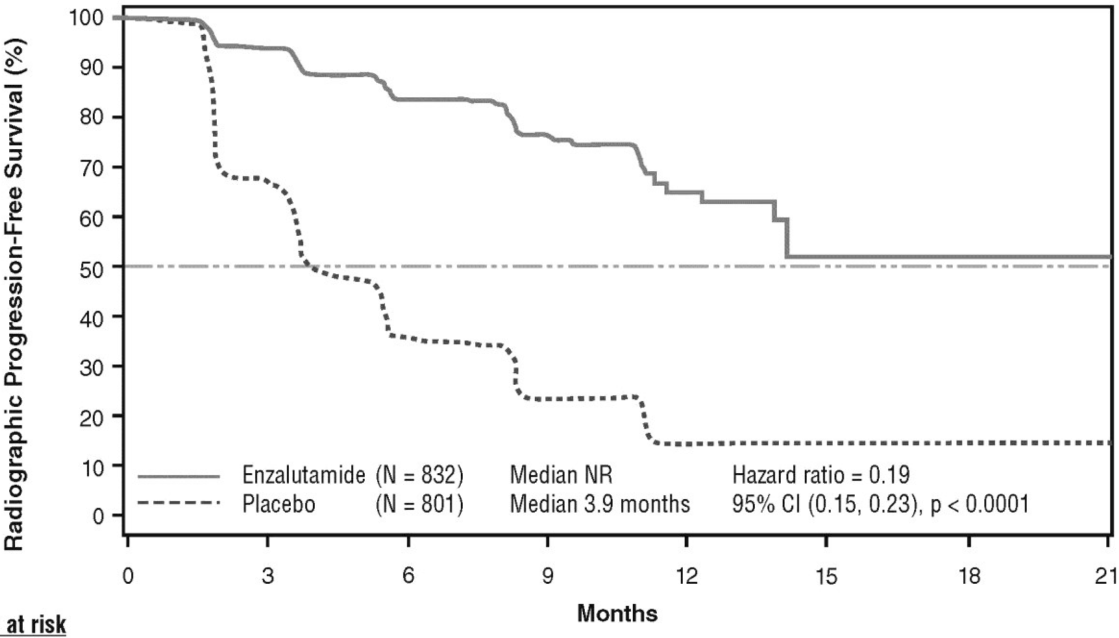


Figure 10: 5-year overall survival analysis by subgroup: Hazard ratio and 95% Confidence Interval in the PREVAIL study (intent-to-treat analysis)



At the pre-specified rPFS analysis, a statistically significant improvement was demonstrated between the treatment groups with an 81.4% reduction in risk of radiographic progression or death [HR = 0.19 (95% CI: 0.15, 0.23), p < 0.0001]. One hundred and eighteen (14%) enzalutamide-treated patients and 321 (40%) of placebo-treated patients had an event. The median rPFS was not reached (95% CI: 13.8, not reached) in the enzalutamide-treated group and was 3.9 months (95% CI: 3.7, 5.4) in the placebo-treated group (Figure 11). Consistent rPFS benefit was observed across all pre-specified patient subgroups (e.g., age, baseline ECOG performance, baseline PSA and LDH, Gleason score at diagnosis, and visceral disease at screening). A pre-specified follow-up rPFS analysis based on the investigator assessment of radiographic progression demonstrated a statistically significant improvement between the treatment groups with a 69.3% reduction in risk of radiographic progression or death [HR = 0.31 (95% CI: 0.27, 0.35), p < 0.0001]. The median rPFS was 19.7 months in the enzalutamide group and 5.4 months in the placebo group.

Figure 11: Kaplan-Meier curves of radiographic progression-free survival in the PREVAIL study (intent-to-treat analysis)



Patients at risk								
Enzalutamide	832	501	240	119	32	5	1	0
Placebo	801	280	65	12	2	0	0	0

At the time of the primary analysis there were 1633 patients randomized.

In addition to the co-primary efficacy endpoints, statistically significant improvements were also demonstrated in the following prospectively defined endpoints.

The median time to initiation of cytotoxic chemotherapy was 28.0 months for patients receiving enzalutamide and 10.8 months for patients receiving placebo [HR = 0.35 (95% CI: 0.30, 0.40), $p < 0.0001$].

The proportion of enzalutamide-treated patients with measurable disease at baseline who had an objective soft tissue response was 58.8% (95% CI: 53.8, 63.7) compared with 5.0% (95% CI: 3.0, 7.7) of patients receiving placebo. The absolute difference in objective soft tissue response between enzalutamide and placebo arms was [53.9% (95% CI: 48.5, 59.2), $p < 0.0001$]. Complete responses were reported in 19.7% of enzalutamide-treated patients compared with 1.0% of placebo-treated patients, and partial responses were reported in 39.1% of enzalutamide-treated patients versus 3.9% of placebo-treated patients.

Enzalutamide significantly decreased the risk of the first skeletal-related event by 28% [HR = 0.718 (95% CI: 0.61, 0.84) $p < 0.0001$]. A skeletal-related event was defined as radiation therapy or surgery to bone for prostate cancer, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain. The analysis included 587 skeletal-related events, of which 389 events (66.3%) were radiation to bone, 79 events (13.5%) were spinal cord compression, 70 events (11.9%) were pathologic bone fracture, 45 events (7.6%) were change in antineoplastic therapy to treat bone pain, and 22 events (3.7%) were surgery to bone.

Patients receiving enzalutamide demonstrated a significantly higher total PSA response rate (defined as a ≥ 50% reduction from baseline), compared with patients receiving placebo, 78.0% versus 3.5% (difference = 74.5%, $p < 0.0001$).

The median time to PSA progression per PCWG2 criteria was 11.2 months for patients treated with enzalutamide and 2.8 months for patients who received placebo [HR = 0.17, (95% CI: 0.15, 0.20), $p < 0.0001$].

Treatment with enzalutamide decreased the risk of FACT-P degradation by 37% compared with placebo ($p < 0.0001$). The median time to degradation in FACT-P was 11.3 months in the enzalutamide group and 5.6 months in the placebo group.

CRPC2 (AFFIRM) study (patients with metastatic CRPC who previously received chemotherapy)

The efficacy and safety of enzalutamide in patients with metastatic castration-resistant prostate cancer who had received docetaxel and were using a luteinising hormone-releasing hormone (LHRH) analogue or had undergone orchiectomy were assessed in a randomised, placebo-controlled, multicentre phase 3 clinical trial. A total of 1,199 patients were randomised 2:1 to receive either enzalutamide orally at a dose of 160 mg once daily (N = 800) or placebo once daily (N = 399). Patients were allowed but not required to take prednisone (maximum daily dose allowed was 10 mg prednisone or equivalent). Patients randomised to either arm were to continue treatment until disease progression (defined as confirmed radiographic progression or the occurrence of a skeletal-related event) and initiation of new systemic antineoplastic treatment, unacceptable toxicity, or withdrawal.

The following patient demographics and baseline disease characteristics were balanced between the treatment arms. The median age was 69 years (range 41-92) and the racial distribution was 93% Caucasian, 4% Black, 1% Asian, and 2% Other. The ECOG performance score was 0-1 in 91.5% of patients and 2 in 8.5% of patients; 28% had a mean Brief Pain Inventory score of ≥ 4 (mean of patient's reported worst pain over the previous 24 hours calculated for seven days prior to randomization). Most (91%) patients had metastases in bone and 23% had visceral lung and/or liver involvement. At study entry, 41% of randomized patients had PSA progression only, whereas 59% of patients had radiographic progression. Fifty-one percent (51%) of patients were on bisphosphonates at baseline.

The AFFIRM study excluded patients with medical conditions that may predispose them to seizures (see section 4.8) and medicinal products known to decrease the seizure threshold, as well as clinically significant cardiovascular disease such as uncontrolled hypertension, recent history of myocardial infarction or unstable angina, New York Heart Association class III or IV heart failure (unless ejection fraction was ≥ 45%), clinically significant ventricular arrhythmias or AV block (without permanent pacemaker).

The protocol pre-specified interim analysis after 520 deaths showed a statistically significant superiority in overall survival in patients treated with enzalutamide compared to placebo (Table 5 and Figure 12 and 13).

Table 5: Overall survival of patients treated with either enzalutamide or placebo in the AFFIRM study (intent-to-treat analysis)

	Enzalutamide (N = 800)	**Placebo (N = 399)**
Deaths (%)	308 (38.5%)	212 (53.1%)
Median survival (months) (95% CI)	18.4 (17.3, NR)	13.6 (11.3, 15.8)
P-value[1]	p < 0.0001	
Hazard ratio (95% CI)[2]	0.63 (0.53, 0.75)	

NR = Not Reached.

1. P-value is derived from a log rank test stratified by ECOG performance status score (0-1 vs. 2) and mean pain score (< 4 vs. ≥ 4).
2. Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio < 1 favours enzalutamide.

Figure 12: Kaplan-Meier curves of overall survival in the AFFIRM study (intent-to-treat analysis)

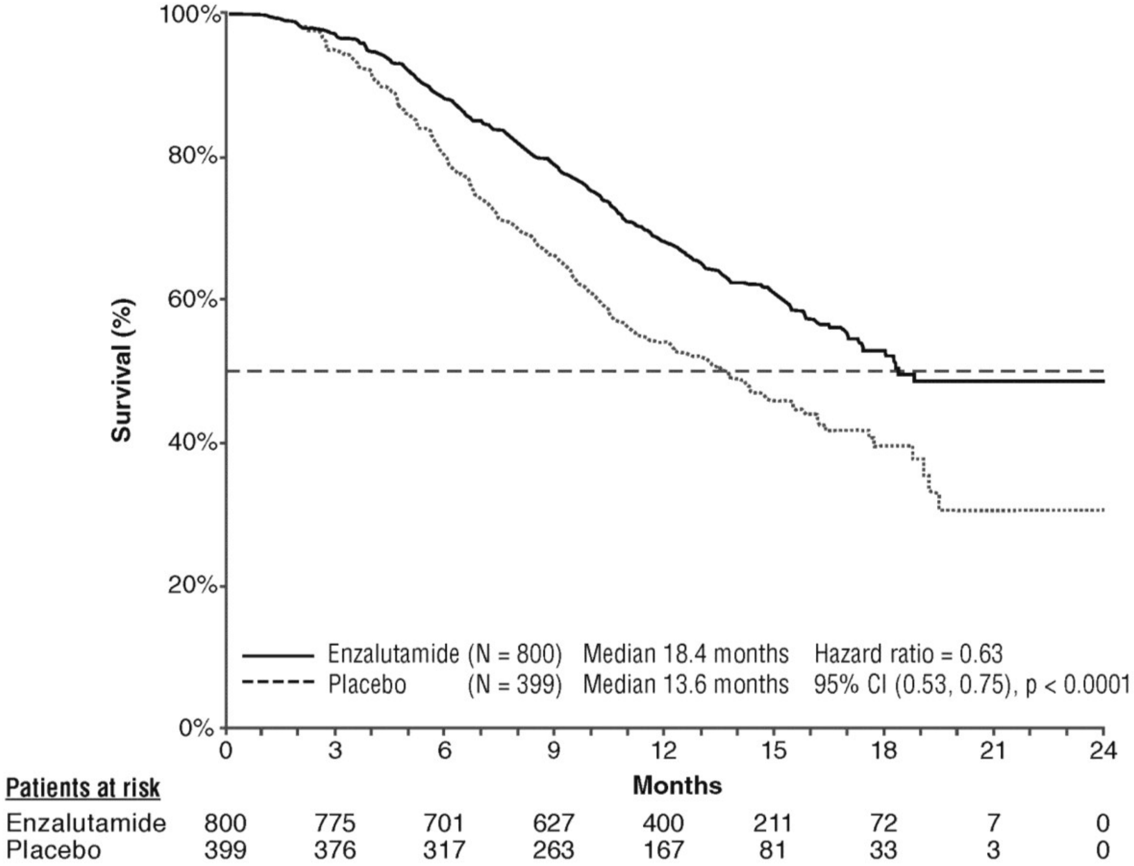
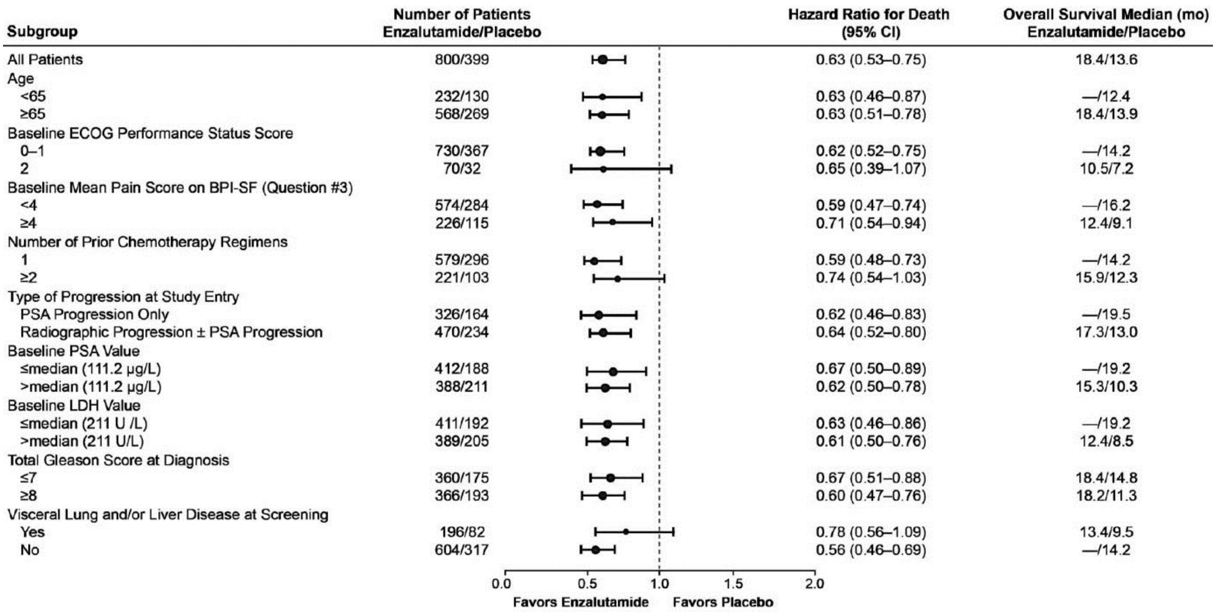


Figure 13: Overall survival by subgroup in the AFFIRM study – Hazard ratio and 95% confidence interval



ECOG: Eastern Cooperative Oncology Group; BPI-SF: Brief Pain Inventory-Short Form; PSA: Prostate Specific Antigen

In addition to the observed improvement in overall survival, key secondary endpoints (PSA progression, radiographic progression-free survival, and time to first skeletal-related event) favoured enzalutamide and were statistically significant after adjusting for multiple testing.
Radiographic progression-free survival as assessed by the investigator using RECIST v1.1 for soft tissue and appearance of 2 or more bone lesions in bone scan was 8.3 months for patients treated with enzalutamide and 2.9 months for patients who received placebo [HR = 0.40 (95% CI: 0.35, 0.47), $p < 0.0001$]. The analysis involved 216 deaths without documented progression and 645 documented progression events, of which 303 (47%) were due to soft tissue progression, 268 (42%) were due to bone lesion progression and 74 (11%) were due to both soft tissue and bone lesions.

Confirmed PSA decline of 50% or 90% were 54.0% and 24.8%, respectively, for patients treated with enzalutamide and 1.5% and 0.9%, respectively, for patients who received placebo ($p < 0.0001$). The median time to PSA progression was 8.3 months for patients treated with enzalutamide and 3.0 months for patients who received placebo [HR = 0.25 (95% CI: 0.20, 0.30), $p < 0.0001$].

The median time to first skeletal-related event was 16.7 months for patients treated with enzalutamide and 13.3 months for patients who received placebo [HR = 0.69 (95% CI: 0.57, 0.84), $p < 0.0001$]. A skeletal-related event was defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain. The analysis involved 448 skeletal-related events, of which 277 events (62%) were radiation to bone, 95 events (21%) were spinal cord compression, 47 events (10%) were pathologic bone fracture, 36 events (8%) were change in anti-neoplastic therapy to treat bone pain and 7 events (2%) were surgery to bone.

Elderly
Of the 4168 patients in the controlled clinical trials who received enzalutamide, 3265 patients (78%) were 65 years and over and 1469 patients (35%) were 75 years and over. No overall differences in safety or effectiveness were observed between these older patients and younger patients.

5.2 Pharmacokinetic properties

Enzalutamide is poorly water soluble. In this product, the solubility of enzalutamide is increased by caprylocaproyl macrogolglycerides as emulsifier/surfactant. In preclinical studies, the absorption of enzalutamide was increased when dissolved in caprylocaproyl macrogolglycerides.

The pharmacokinetics of enzalutamide have been evaluated in prostate cancer patients and in healthy male subjects. The mean terminal half-life ($t_{1/2}$) for enzalutamide in patients after a single oral dose is 5.8 days (range 2.8 to 10.2 days), and steady state is achieved in approximately one month. With daily oral administration, enzalutamide accumulates approximately 8.3-fold relative to a single dose. Daily fluctuations in plasma concentrations are low (peak-to-trough ratio of 1.25). Clearance of enzalutamide is primarily via hepatic metabolism, producing an active metabolite that is equally as active as enzalutamide and circulates at approximately the same plasma concentration as enzalutamide.

Absorption
Maximum plasma concentrations (C_{max}) of enzalutamide in patients are observed 1 to 2 hours after administration. Based on a mass balance study in humans, oral absorption of enzalutamide is estimated to be at least 84.2%. Enzalutamide is not a substrate of the efflux transporters P-gp or BCRP. At steady state, the mean C_{max} values for enzalutamide and its active metabolite are 16.6 μg/mL (23% coefficient of variation [CV]) and 12.7 μg/mL (30% CV), respectively.

Food has no clinically significant effect on the extent of absorption. In clinical trials, Xtandi was administered without regard to food.

Distribution
The mean apparent volume of distribution (V/F) of enzalutamide in patients after a single oral dose is 110 L (29% CV). The volume of distribution of enzalutamide is greater than the volume of total body

water, indicative of extensive extravascular distribution. Studies in rodents indicate that enzalutamide and its active metabolite can cross the blood brain barrier.
Enzalutamide is 97% to 98% bound to plasma proteins, primarily albumin. The active metabolite is 95% bound to plasma proteins. There is no protein binding displacement between enzalutamide and other highly bound drugs (warfarin, ibuprofen and salicylic acid) *in vitro.*

Biotransformation
Enzalutamide is extensively metabolized. There are two major metabolites in human plasma: N-desmethyl enzalutamide (active) and a carboxylic acid derivative (inactive). Enzalutamide is metabolized by CYP2C8 and to a lesser extent by CYP3A4/5 (see section 4.5), both of which play a role in the formation of the active metabolite. *In vitro*, N-desmethyl enzalutamide is metabolized to the carboxylic acid metabolite by carboxylesterase 1, which also plays a minor role in the metabolism of enzalutamide to the carboxylic acid metabolite. Carboxylesterase 2 does not appear to play a role in the metabolism of either enzalutamide or N-desmethyl enzalutamide. N-desmethyl enzalutamide was not metabolized by CYPs *in vitro*.

Under conditions of clinical use, enzalutamide is a strong inducer of CYP3A4, a moderate inducer of CYP2C9 and CYP2C19, and has no clinically relevant effect on CYP2C8 (see section 4.5).

Elimination
The mean apparent clearance (CL/F) of enzalutamide in patients ranges from 0.520 and 0.564 L/h.

Following oral administration of ^{14}C-enzalutamide, 84.6% of the radioactivity is recovered by 77 days post dose: 71.0% is recovered in urine (primarily as the inactive metabolite, with trace amounts of enzalutamide and the active metabolite), and 13.6% is recovered in faeces (0.39% of dose as unchanged enzalutamide).

In vitro data indicate that enzalutamide is not a substrate for OATP1B1, OATP1B3, or OCT1; and N-desmethyl enzalutamide is not a substrate for P-gp or BCRP.

In vitro data indicate that enzalutamide and its major metabolites do not inhibit the following transporters at clinically relevant concentrations: OATP1B1, OATP1B3, OCT2, or OAT1.

Linearity
No major deviations from dose proportionality are observed over the dose range 40 to 160 mg. The steady-state C_{min} values of enzalutamide and the active metabolite in individual patients remained constant during more than one year of chronic therapy, demonstrating time-linear pharmacokinetics once steady-state is achieved.

Renal impairment
No formal renal impairment study for enzalutamide has been completed. Patients with serum creatinine > 177 µmol/L (2 mg/dL) were excluded from clinical studies. Based on a population pharmacokinetic analysis, no dose adjustment is necessary for patients with calculated creatinine clearance (CrCL) values ≥ 30 mL/min (estimated by the Cockcroft and Gault formula). Enzalutamide has not been evaluated in patients with severe renal impairment (CrCL < 30 mL/min) or end-stage renal disease, and caution is advised when treating these patients. It is unlikely that enzalutamide will be significantly removed by intermittent haemodialysis or continuous ambulatory peritoneal dialysis.

Hepatic impairment
Hepatic impairment did not have a pronounced effect on the total exposure to enzalutamide or its active metabolite. The half-life of enzalutamide was however doubled in patients with severe hepatic impairment compared with healthy controls (10.4 days compared to 4.7 days), possibly related to an increased tissue distribution.

The pharmacokinetics of enzalutamide were examined in subjects with baseline mild (N = 6), moderate (N = 8), or severe (N=8) hepatic impairment (Child-Pugh Class A, B or C, respectively) and in 22-matched control subjects with normal hepatic function. Following a single oral 160 mg dose of enzalutamide, the AUC and C_{max} for enzalutamide in subjects with mild impairment increased by 5% and 24%, respectively, the AUC and C_{max} of enzalutamide in subjects with moderate impairment increased by 29% and decreased by 11%, respectively, and the AUC and C_{max} of enzalutamide in subjects with severe impairment increased by 5% and decreased by 41%, respectively, compared to healthy control subjects. For the sum of unbound enzalutamide plus the unbound active metabolite, the AUC and C_{max} in subjects with mild impairment increased by 14% and 19%, respectively, the AUC and C_{max} in subjects with moderate impairment increased by 14% and decreased by 17%, respectively, and the AUC and C_{max} in subjects with severe hepatic impairment increased by 34% and decreased by 27%, respectively, compared to healthy control subjects.

Race
Most patients in the controlled clinical studies (> 77%) were Caucasian. Based on pharmacokinetic data from studies in Japanese and Chinese patients with prostate cancer, there were no clinically relevant differences in exposure among the populations. There are insufficient data to evaluate potential differences in the pharmacokinetics of enzalutamide in other races.

Elderly
No clinically relevant effect of age on enzalutamide pharmacokinetics was seen in the population pharmacokinetic analysis.

5.3 Preclinical safety data

Enzalutamide treatment of pregnant mice resulted in an increased incidence of embryo-fetal deaths and external and skeletal changes. Fertility studies were not conducted with enzalutamide, but in studies in rats (4 and 26 weeks) and dogs (4, 13 and 39 weeks), atrophy, aspermia/hypospermia, and hypertrophy/hyperplasia in the reproductive system were noted, consistent with the pharmacological activity of enzalutamide. In studies in mice (4 weeks), rats (4 and 26 weeks) and dogs (4, 13 and 39 weeks), changes in the reproductive organs associated with enzalutamide were decreases in organ weight with atrophy of the prostate and epididymis. Leydig cell hypertrophy and/or hyperplasia were observed in mice (4 weeks) and dogs (39 weeks). Additional changes to reproductive tissues included hypertrophy/hyperplasia of the pituitary gland and atrophy in seminal vesicles in rats and testicular hypospermia and seminiferous tubule degeneration in dogs. Gender differences were noted in rat mammary glands (male atrophy and female lobular hyperplasia). Changes in the reproductive organs in both species were consistent with the pharmacological activity of enzalutamide and reversed or partially resolved after an 8-week recovery period. There were no other important changes in clinical pathology or histopathology in any other organ system, including the liver, in either species.

Studies in pregnant rats have shown that enzalutamide and/or its metabolites are transferred to fetuses. After oral administration of radiolabeled ^{14}C-enzalutamide to rats on Day 14 of pregnancy at a dose of 30 mg/kg, the maximum radioactivity in the fetus was reached 4 hours after administration and was lower than that in the maternal plasma with tissue/plasma ratio of 0.27. Radioactivity in the fetus decreased to 0.08 times the maximum concentration at 72 hours after administration.

Studies in lactating rats have shown that enzalutamide and/or its metabolites are secreted in rat milk. After oral administration of radiolabeled ^{14}C-enzalutamide to lactating rats at a dose of 30 mg/kg, the maximum radioactivity in the milk was reached 4 hours after administration and was up to 3.54-fold higher than that in the maternal plasma. Study results also have shown that enzalutamide and/or its metabolites are transferred to infant rat tissues via milk and subsequently eliminated.

Enzalutamide was negative for genotoxicity in a standard battery of *in vitro* and *in vivo* tests. In a 6-month study in transgenic rasH2 mice, enzalutamide did not show carcinogenic potential (absence of neoplastic findings) at doses up to 20 mg/kg per day (AUC_{24h} ~317 μg·h/mL), which resulted in plasma exposure levels similar to the clinical exposure (AUC_{24h} ~322 μg·h/mL) in mCRPC patients receiving 160 mg, daily.

Daily dosing of rats for two years with enzalutamide at 10–100 mg/kg/day produced an increased incidence of neoplastic findings (compared to control) that were considered related to the primary pharmacology of enzalutamide. These included benign thymoma, fibroadenoma in the mammary glands, and benign Leydig cell tumors in the testes in males; benign granulosa cell tumor in the ovaries in females; and adenoma in the pars distalis of the pituitary in both sexes. The most prominent of these were benign Leydig cell tumours, urothelium papilloma, and carcinoma of urinary bladder. Benign Leydig cell tumours in rats are generally not considered relevant to humans based on experience with other anti-androgens. Urothelium papilloma and carcinoma of urinary bladder in male rats were observed at the 100 mg/kg/day dose and were considered secondary to the irritation caused by the increased urinary crystal/calculi expected in rats based on the horizontal structure of the rat urinary bladder. Other tumours, which are also potentially related to the primary pharmacology include fibroadenoma of mammary glands and benign thymoma of thymus in males, benign granulosa cell tumours of ovaries in females, and adenoma of pituitary pars distalis in both sexes. The human relevance of thymoma, pituitary adenoma and fibroadenoma in rats is unclear, but a potential relevance cannot be ruled out. The exposure levels achieved in this study in male rats at Week 26 at 100 mg/kg per day for enzalutamide plus its active metabolites M1 and M2 (AUC_{24}: enzalutamide ~457 µg·h/mL, M1 ~321 µg·h/mL, M2 ~35 µg·h/mL) were less than or similar to those in prostate cancer patients at the recommended dose (160 mg/day) of enzalutamide (AUC_{24}: enzalutamide ~322 µg·h/mL, M1 ~193 µg·h/mL, M2 ~278 µg·h/mL).

Enzalutamide was not phototoxic *in vitro*.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

<u>Capsule contents</u>
Caprylocaproyl macrogol-8 glycerides
Butylhydroxyanisole (E320)
Butylhydroxytoluene (E321)

<u>Capsule shell</u>
Gelatin
Sorbitol sorbitan solution
Glycerol
Titanium dioxide (E171)
Purified water

<u>Printing ink</u>
Iron oxide black (E172)
Polyvinyl acetate phthalate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

PVC/PCTFE/Aluminium blister of 4 soft capsules in an aluminium pouch.
Box of 7 aluminium pouches (28 soft capsules)

Box of 14 aluminium pouches (56 soft capsules)
Box of 28 aluminium pouches (112 soft capsules)

6.6 Special precautions for disposal and other handling

Xtandi should not be handled by persons other than the patient or his caregivers. The soft capsules should not be dissolved or opened.

Based on its mechanism of action and embryo-fetal toxicity observed in mice, enzalutamide may harm a developing fetus. Women who are or may become pregnant should not handle damaged or opened enzalutamide capsules without protection, e.g., gloves (See section 5.3).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Keep out of the reach of children.

7. Manufacturer

Catalent Pharma Solutions, LLC
2725 Scherer Drive
St. Petersburg, FL 33716, USA

8. Date of Revision of Package Insert

August 2021 (CCDS V7.0)

For any enquiry, please write to pv@sg.astellas.com.